Cytokine mRNA Profile Of Myelin Basic Protein Reactive T-Cells In Multiple Sclerosis

Vandevyver C; Motmans K; Stinissen P; Zhang J; Raus J
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Department of Immunology,
Dr. L. Willems-Instituut,
Universitaire Campus, Diepenbeek,
Belgium

UI # 98442976,
Abstract

AutoImmune mechanisms involving T-Cell responses to (a) Myelin AutoAntigen(s), such as Myelin Basic Protein (MBP), are thought to contribute to the PathoGenesis of Multiple Sclerosis (MS).

Cytokines may play a central role in the regulation of the Pathogenic AutoImmune responses in MS and the mediation of tissue damage in the disease.

To study the Cytokine expression of Myelin reactive T-Cells in MS, we determined the Cytokine mRNA levels in a panel of blood derived MBP-specific T-Cell clones derived from MS patients (33 clones) and normal controls (21 clones), using a novel quantitative RT-PCR method.

Our results demonstrate that MBP-specific T-Cells, both from MS patients and control subjects, predominantly display a Th1- or Th2-like Cytokine pattern. Although MS clones express higher levels of TNFalpha and IL-10 mRNA, these differences do not reach statistical significance.

Interestingly, significantly increased TNFα and IFN-γ mRNA levels were observed among clones derived from HLA-DR2 positive versus HLA-DR2 negative MS patients. This HLA halpotype is known to be associated with MS.

The high levels of TNFα and IFNγ mRNA observed in MBP-reactive T-Cell clones from MS patients indicate an important role of these Cytokines in the disease process. Our data lend further support to the Pathogenic role of MBP-reactive T-Cells in MS.

Medical Texts

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Abstracts

ANS | Bladder | Cognition | Fatigue | Fluid | Genetics
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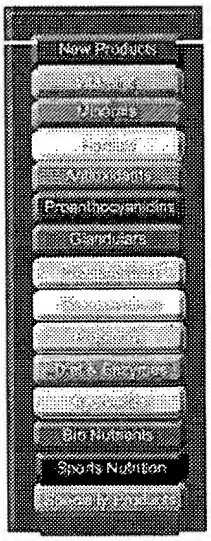

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60 Capsules HI2020 Each Capsule contains Myelin Sheath Extract (Spinal Cord) 235mg Suggested Use Take two capsules a day or as directed by a qualified health care practitioner. Main Applications As reported by literature: -Treatment of MS. -Fibromyalgia. Origin USA. Source Bovine spuigomyelivi. None hormone fed, free-range grazing animals from New Zeland. Pregnant / Nursing Has not been tested, best to avoid use. Interactions None reported.

Multiple Sclerosis and related demyelinating diseases remain one of the unsolved neurological mysteries of our time. This common neurological disorder primarily affects young adults and is more prevalent in persons of Western European lineage living in temperate zones. The disease still remains a puzzle to scientists exploring its causes. Pathologically the disease is characterized by demyelination with reactive gliosis scattered in the white matter of the brain, spinal cord and optic nerve. The common initial presentation includes weakness, numbness, tingling, spastic paraparesis or sphincter disturbances. The disease is characterized by frequent relapses and remissions which lead to increasing disability, weakness, spasticity, impaired vision and urinary incontinence. Approximately 20% of patients with multiple sclerosis have aggressive debilitating symptoms while the remainder may live a normal life. Most treatments for multiple sclerosis (MS) have focused on the use of potentially toxic and immunosuppressive drugs such as steroids and cyclophosphamides. Even the American Medical Association Book of Drug Evaluations provides no specific long-term benefit of these drugs, in recognition of the fact that they do not prevent further relapses. Two major theories of pathogenesis of MS have been proposed. One; that MS is a viral disease of the central nervous system, the inflammatory response in the brain being an anti-viral immune response. And two; that MS is an autoimmune disease in which infiltrating T-cells recognize self-antigens and attack normal tissue. These two possibilities are not mutually exclusive. The autoimmune response may be triggered by environmental factors such as viral infections, however, the inability to transfer the disease to primates or to isolate the virus from CNS tissue of MS patiens, despite tremendous efforts, lends indirect support to the theory that the inflammatory process may be autoimmune in nature. Physical Characteristics of Myelin Myelin is a very important constituent of the white matter of the brain and the myelin sheath forms 50 per cent of the total dry weight. Myelin is mainly responsible for the gross chemical differences between white and Gray matter and accounts for the glistening white appearance and high lipid content of the white matter. The myelin sheath is a greatly extended and modified plasma membrane that is wrapped around the nerve axon in a spiral fashion. Myelin acts as an electrical insulator surrounding the axon, the "wire" carrying the current. Myelin also facilitates nerve conduction. This lipid-rich material contains high concentrations of cholesterol, phospholipids and plasmalogens. The basic proteins in myelin sheath are immunologically active and may cause an antibody response. Although early experiments used injections of Myelin Basic Protein (MBP) recent studies suggest that the protein is active while taken orally. Immunologists now know the cellular

mechanisms which justify the use of myelin sheath extract in clinical practice. The Peyer's patches in the intestine contain the immunological receptor sites which recognize myelin basic protein. When a glandular extract of myelin sheath is taken orally in a patient with multiple sclerosis, the protein appears in the epithelial cells that line the lower small intestine. As a person's T-cells circulate through the intestinal wall, complement cells that recognize MBP bind to these epithelial cells and are somehow inactivated. Receptors in the gut may signal the body to stop attacking its own myelin sheath. This basic premise forms the scientific justification for the use of the glandular extract. Immunolgical Correlates Mechanism of Action Immunological tolerance is defined as a state of specific immunologic Cont. next page EAE-DefinitiveExperimentalModel Recently, Howard Weiner and co-workers at Harvard Medical School have demonstrated that the potent suppressive effects of oral tolerance can be extended to the autoimmune disease, experimental autoimmune encephalomyelitis (EAE). EAE has frequently been studied as a model for the human demyelinating diseased, particularly multiple sclerosis. Suppression of both the acute and relapsing episodes has been one of the major goals of research of multiple sclerosis. Therapeutic strategies used to suppress EAE include treatment with immunosuppressive drugs such as cyclophospamide and cyclosporin, or injection of monoclonal antibodies directed against T-cell subsets. Oral administration of myelin basic protein (MBP) prior to EAE induction results in a profound suppression of clinical signs, a significant decrease in EAE hisopathological changes and virtually absent lymphocyte-proliferate responses to MBP. It is clear that myelin basic protein also elicits production of an antibody which has been implicated as a participating factor in demyelination events. MBP-induced oral tolerance in EAE profoundly suppresses the clinical neuralgic signs, delays the onset of symptoms and significantly reduces the extent of mononuclear cell infiltration into the central nervous system. The oral introduction of antigen is known to readily reduce tolerance and result in the systemic suppression of both antibody and cell-mediated immune responses. Carol Witacre and co-workers at Ohio State Medical School have provided evidence for the potent effects of orally introduced antigen in the autoimmune disease EAE. Not only were in vitro lymphocyte proliferative responses significantly decreased in an antigen-specific manner following the oral administration of MBP, but the incidence and severity of both the clinical and the histopathological manifestations of EAE were unresponsiveness to an agent after exposure to the agent. An effective and long recognized method of inducing immunologic tolerance is the oral administration of the antigen, which was first demonstrated by Wells for hen's egg proteins in 1911. Orally induced tolerance is a normal immune response that is considered to function in the prevention of allergic and autoimmune reactions to food antigens. Although the oral administration has been widely studied as a means of suppressing the immune response for a number of different cellular, protein and non-protein (e.g. contact-sensitizing) antigens, it has not been applied in the suppression of autoimmune disease to a defined antigen until recently. Adoptive transfer studies with animals fed other antigens have often shown that antigen-specific suppressor T-cells are generated by feeding and are involved in actively suppressing the immune response. One of the primary goals for the treatment of cell mediated autoimmune diseases is to specifically suppress autoreactive T-cells. Other mechanisms, such as the production of soluble factors in the serum and the formation of antigen-antibody complexes have also been proposed and may represent additional or alternative mechanisms. Oral induction of tolerance to autoantigens may provide a nontoxic, immunologically specific therapy

for suppressing ongoing autoimmune processes in a variety of clinical conditions in which candidate autoantigens have been identified. markedly diminished. The specificity, or the orally induced tolerance to MBP has been found to be strikingly species-dependent with regard to the induction of clinical EAE. For example, tolerance resulting from oral guinea pig MBP is only effective in protecting rats against a MBP challenge and the same degree of specificity was observed for human MBP. However, attempting to orally tolerize rats against the self-antigen RMBP is unsuccessful. It has been shown that following ingestion of protein antigens, minute amounts of these antigens are absorbed and circulate either in native protein form or in immune complexes. With continued exposure, a state of mucosal immunity develops concomitantly with active suppression of the systemic immune response. It is possible that the mechanisms in place to maintain tolerance to self antigens in the rat either prevent the absorption of MBP from the gastrointestinal tract or, more likely, prevent the local mucosal immune response. The application of oral tolerance to other models of autoimmune disease has recently received attention, including the suppression of type II collagen-induced arthritis, systemic lupus erythematosus and uveitis. A variety of mechanisms have been described for the maintenance of self-tolerance in the host. One major focus of study is the antigen-driven active suppression after oral administration of antigens as a tolerance mechanism and as a method to down-regulate autoimmune diseases. Oral tolerance to autoantigens is both disease and antigen specific. Feeding MBP suppresses EAE but does not affect experimental autoimmune uveitis or rheumatoid arthritis. Similarly, feeding type II collagen suppresses arthritis models but not EAE. Thus, the secretion and action of antigen-nonspecific factors by regulatory cells induced by oral tolerance must occur in the local microenvironment of the lymphoid tissue where the immune response is generated, along migratory pathways of the effector cells and/or at the inflamed site in the target organ where the autoantigen is present. Studies are currently in progress to further elucidate the temporal sequence and location of these interactions between regulatory and effector cells. Use of Purified Glandular Extracts in Other Autoimmune Diseases The model for the efficacy in using oral extracts of type II collagen in rheumatoid arthritis has recently been elucidated. The mechanism for such suppression relates to the generation of collagen specific suppressor cells that are generated by feeding and that migrate to the joint where they are triggered by collagen to Continued release antigen-nonspecific suppressor cytokines. Similar results have been found in the suppression of diabetes by feeding oral insulin from pancreatic tissue. Thus, the treatment of an organ-specific autoimmune disease by oral tolerization may not require knowledge of the inciting autoantigen, only the oral administration of an autoantigen from the target organ. MBP comprises 30% of the polypeptides of CNS myelin. Detection of MBP peptides in cerebrospinal fluid may indicate ongoing CNS demyelination. How MBP leaves its intracellular location to become accessible to auto-aggression lymphocytes within the CNS is a long-standing question. References

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Phar 441 Immunology

Hermann v. Grafenstein

Lecture 10 - Autoimmune diseases

Definition: Although the immune system normally defends its host against infectious pathogens without reacting to self, this distinction is not always maintained. Thus, autoimmune diseases are a consequence of detrimental immune reactions to self.

8.1. Introduction

Why can this occur? As outlined In previous lectures, recognition of antigen by the adaptive immune system is mediated by highly diverse, clonally distributed receptors. The molecular diversity of these receptors is generated by essentially random recombination of gene segments or nucleotide additions between these gene segments. This applies to both, antibody and T cell receptor genes. Antibody genes can in addition undergo somatic mutations. Because the randomness of these diversity generating mechanisms does not exclude specificities that are directed to self, the potential to autoimmunity exists. In normal situations tolerance to self is maintained by either clonal deletion of autoreactive lymphocytes early during their development in central lymphoid organs or later in the periphery. It is very likely that even the combination of central and peripheral tolerance is incomplete and allows autoreactive lymphocytes to exist. These lymphocytes may never meet the self antigen they recognize, but if they are activated for some reason, they can give rise to autoimmunity.

8.2. Classification of autoimmune diseases

Autoimmune reactions can occur to almost every tissue in the body, sometimes to more than one tissue simultaneously. Most autoimmune diseases where known clinically long before their autoimmune etiology was uncovered. They are classified according to the tissue that is affected. Systemic autoimmune diseases affect more than one tissue in contrast to organ specific autoimmune diseases. Table 8.1 gives an overview of some of the more common autoimmune diseases, listing the affected organ and some of the major symptoms.

Table 8.1. Common Autoimmune diseases and their symptoms

Disease	Primary organ(s) affected	Major symptoms
Rheumathoid arthritis	Joints	Pain & inflammation, deformity

Systemic lupus erythematosus	Multi-organ disease (joints, skin, kidneys, cardiopulmonary, central nervous system, lymph nodes, spleen, liver	Joint pain and inflammation but usually no deformities, skin rash, proteinurea to renal failure, lupus pneumonitis, narrowing of coronary arteries, convulsions
Type I diabetes	Insulin producing pancreatic β-cells	Hypoglycemia, dependence on daily insulin injections
Graves' disease	Thyroid	Goiter with hyperthyroidism, ophthalmopathy (exophthalmus), dermopathy (localized thickening of skin)
Myasthenia gravis	Acetylcholine receptor in neuromuscular junctions	Weakness, undue fatiguability on exercise
Hashimoto's thyroiditis	Thyroid	Goiter often associated with hypothyroidism
Pemphigus vulgaris	Desmoglein 3	Skin blister formation
Ankylosing spondylitis	Articulations of spine and adjacent soft tissue	Back pain, progressive stiffness, "bent over posture"
Goodpasture's syndrome	Non-collagenous domain of basement membrane collagen type IV	Vasculitis, renal failure
Multiple sclerosis	Myelin sheets of nerve (myelin basic protein, proteolipid protein)	Paralysis

8.3. Effector mechanisms involved in autoimmune diseases

Autoimmune responses use all known types of effector mechanisms that lead to tissue damage in hypersensitivity reactions to external antigens, perhaps with the exception of IgE mediated type I hypersensitivity reactions. The types of immune responses leading to various autoimmune diseases are summarized in Table 8.2.

Table 8.2 Classification of autoimmune disease according to the pathogenic effector mechanism

Disease	Autoantigen	Consequence
Type II - antibody to surface or matrix antigens		
Autoimmune hemolytic anemia	Rh blood group, I antigen	Destruction of red blood cells by complement and phagocytes, anemia
Autoimmune thrombocytopenic purpura	Platelet integrin gpIIb:IIIa	Abnormal bleeding
Goodpasture's syndrome	Non-collagenous domain of basement membrane collagen type IV	Vasculitis, renal failure
Pemphigus vulgaris	Epidermal cadherin	Blistering of skin
Acute rheumatic fever	Streptococcal cell wall antigens, antigens cross-react with cardiac muscle	Arthritis, myocarditis, late scarring of heart valves
Type III, Immune-complex disease		
Post-streptococcal glomerulonephritis	Streptococcal antigen	Transient nephrotic syndrome
Polyarteritis nodosa	Hepatitis surface antigen	Systemic vasculitis
Systemic lupus erythematosus	DNA, histones, ribosomes, snRNP, scRNP	Glomerulonephritis, vasculitis, arthritis
Type IV - T-cell mediated disease		
Type I diabetes	Unknown pancreatic β-cell autoantigen	β-cell destruction
Rheumathoid arthritis	Unknown synovial joint antigen	Joint inflammation and destruction
Multiple sclerosis, experimental autoimmune encephalomyelitis (EAE)	Myelin basic protein, proteolipid protein	Brain invasion by CD4 T cells, paralysis

As is apparent from Table 8.2, autoimmune responses are antibody mediated or mediated by inflammatory T cells. One would expect a dominance of Th2 cells for type II and type III responses and a dominance of Th1 cells in type IV responses. Evidence is accumulating that this dichotomy does indeed apply. it appears for example that during phases of

exasperation of multiple sclerosis, Th1 cells become more activated, whereas in phases of remission, Th2 cells predominate in lesions.

Antibodies can cause disease in many different ways. Interestingly, they can not only opsonize cells for phagocytosis or block receptors, but can stimulate receptors, leading to pathologic activation of endocrine cells (Table 8.3)

Table 8.3, diseases mediated by antibodies to cellular receptors

Syndrome	Antigen	Consequence
Grave's disease	Thyroid stimulating hormone receptor	Hyperthyroidism
Myasthenia gravis	Acetylcholine receptor	Progressive weakness
Insulin resistant diabetes	Insulin receptor (antagonist)	Hypoglycemia. ketoacidosis
Hypoglycemia	Insulin receptor (agonist)	Hypoglycemia

Anti-DNA antibodies in systemic lupus erythematosus: Why autoantibodies arise is not known in most cases. The Figure on the following page explains, how T cells might provide help for the production of anti-native DNA antibodies that are present in systemic lupus erythematosus.

8.4. Etiology of autoimmune diseases

Mechanisms of tolerance and its breakdown

Deletion, ignorance and suppression: After the discovery that central tolerance is incomplete, the question how peripheral tolerance is established and maintained became a major focus of research. In fact, some researchers now believe that we are only tolerant to the most common self antigens that are expressed in the thymus or bone marrow at sufficiently high concentrations to trigger deletion of T or B cells that recognize these self antigens (deletion). Out of all self antigens only very few are deleting. Thus we are not tolerant to most self antigens. Two complementary explanations have been proposed to account the absence of autoimmune disease in healthy individuals despite the open nature of the immune repertoire. One is that it is very hard to evoke immune responses. Transport of antigens to lymphoid organs and presentation by professional APCs is necessary which have to be induced to express co-stimulatory activity. As a consequence, we do not react to many self antigens, although we have lymphocytes specific for them (immunological ignorance). The other explanation postulates that immune responses can not only be induced, but can also effectively downregulated (suppression). Recently some of the endogenous factors that suppress T cells have been identified. Transforming growth factor (**TGF-**β) is one of them.

Immunoprivileged sites: TGF-β is produced by several tissues known to be "**immunoprivileged sites**". Immunoprivileged sites are defined by the observation that grafts or antigens placed within them are tolerated indefinitely. Examples are the brain, the eye, testis, uterus (fetus), and the hamster cheek pouch.

Oral tolerance: The concept of endogenous immunosuppression or "active tolerance" is further supported by the fact that we become tolerant to antigens that we ingest orally despite being immunogenic when introduced subcutaneously. Oral tolerance is an active phenomenon as it can be transferred to non-tolerant animals by T cells from a tolerant animal. Recently T cells have been cloned from gut lymphoid tissue (Peyer's patches) and found to produce TGF-β. The induction of oral tolerance is presently being tested for autoantigens that are known to be the targets of autoimmune diseases (insulin, myelin basic protein and others).

Despite the rapid progress of immunological theory in recent years, a precise mechanistic understanding of the primary cause is not available for any autoimmune disease. Autoimmune diseases are thought to be of multifactorial origin, involving genetic, hormonal, infections and other environmental factors.

8.4.1 Genetic factors

It is clear however that in most cases genetic factors play a role, most notably HLA (MHC) genes. This is plausible as MHC genes play a key role in antigen specific T cell activation. Linkage to certain MHC alleles is usually determined by measuring the frequency of specific MHC alleles in patients afflicted with an autoimmune disease compared to the general population. Vice versa, statistical association of a disease with MHC alleles is often used as one of the criteria that point to an autoimmune etiology.

8.4.2 Hormonal status

MHC genes are by no means the only determinants of autoimmunity. The often striking sex preference suggests that the hormonal status plays a critical role. Furthermore, autoimmune diseases often change during changes of hormonal status such as puberty, pregnancy and menopause. Table 8.4 gives an overview of the HLA association and sex preference of some common autoimmune diseases.

Table 8.4. HLA association and sex preference of some common autoimmune diseases.

Disease	HLA allele	Relative risk	Sex ratio (female / male)
Rheumathoid arthritis	DR4	4.2	3
Systemic lupus erythematosus	DR3	5.8	10-20
Type I diabetes	DR3 and DR4	3.2	~ 1
Graves' disease	DR3	3.7	4-5

Myasthenia gravis	DR3	2.5	~ 1
Hashimoto's thyroiditis	DR5	3.2	~1
Pemphigus vulgaris	DR4	14.4	?
Ankylosing spondylitis	B27	87.4	0.3
Acute anterior uveitis	B27	10.04	<0.5
Goodpasture's syndrome	DR2	15.9	?
Multiple sclerosis	DR2	4.8	10

Studies with identical twins have provided important information about the role of MHC genes in disease susceptibility. Thus, an identical twin of a diabetic child has a 30% chance of developing diabetes, which is far higher than the general population. However, 70% of the twin siblings do not develop disease, suggesting that MHC genes play an important role, but other factors must be important too. The most likely ones are infections and nutrition.

8.4.3 Infections and other environmental factors

Infectious pathogens have been implied in triggering several autoimmune diseases. It is thought that the immune response to a pathogen component crossreacts to a self antigen, a process also known as "molecular mimicry".

8.5. Treatment of autoimmune diseases

8.5.1 Current treatment modalities

The lack of knowledge as to the pathogenic mechanisms of most autoimmune diseases precludes a rational, specific treatment. The present status of treatment is symptomatic or nonspecifically immunosuppressive.

Symptomatic treatment: The designation autoimmune disease refers to a common etiologic origin of a large variety of diseases. Ultimately, the organ system that is affected will determine the clinical symptoms and demand an organ system specific type of treatment.

Examples are: In type I diabetes, daily insulin injections are needed to replace the insulin that can no longer be produced after the destruction of b-cells. In Hashimoto's thyroiditis, thyroid hormone replacement therapy (levothyroxin) may by indicated when the patient becomes hypothyroid, whereas in Graves' disease, the developing hyperthyroidism may be treated with antithyroid agents (e.g. inhibitors of thyroid hormone biosynthesis, such as propylthiouracil or methimazole), and in Myasthenia gravis, neuromuscular transmission may be enhanced by acetylcholine esterase inhibitors (physostigmine).

Immunosuppressive treatment: None of the organ specific treatment modalities are aimed at treating the underlying case of the disease, the autoimmune reaction. In the case of organ

specific autoimmune disease the ideal treatment would target the antigen specific immune response without diminishing responses to unrelated antigens. This should be possible, at least in principle, by targeting only those lymphocytes that express clonally distributed receptors for the autoantigen. This would be the equivalent of antigen specific immuno-stimulation by vaccines, just the reverse. Until now this has not been achieved, although many research laboratories and pharmaceutical companies are trying to develop this ability. At the present time, most of the treatment modalities aimed at controlling the pathogenic immune response are immunosuppressive without being antigen specific. The most common immunosuppressive drugs are listed in Table 8.5.

Table 8.5, Currently used immunosuppressive drugs or drug classes

Steroids

Azathioprine

Cyclophosphamide

Cyclosporine

Methotrexate

These drugs have very different modes of action. Antibody mediated diseases are best treated with steroids and cyclophosphamide. Remission of systemic lupus erythematosus, Wegener's granulomatosis, and Goodpasture's syndrome can be achieved with cyclophosphamide and steroids can be used very effectively in treating systemic lupus erythematosus.

Cyclosporin is a prototype T-cell selective agent and can be used for a large number of autoimmune diseases, particularly autoimmune diseases that employ a type IV, T-cell controlled effector mechanism. Since T cells also control antibody responses, it is not surprising that cyclosporin is also effective in antibody mediated autoimmune diseases.

Autoimmune diseases that can be treated with **cyclosporin**

Type I diabetes

Rheumatoid arthritis

Primary biliary cirrhosis

Diseases with unclear etiology in which the effect of cyclosporin suggests autoimmune etiology

Psoriasis

Nephrotic syndrome

Severe Asthma

Crohn's disease

Antibody and T cell mediated autoimmune diseases are differentially inhibited by immunosuppressive drugs. The following comparison (Table 8.6) illustrates this:

Table 8.6, Differential sensitivity to immunosuppressive agents of antibody and T cell mediated autoimmune diseases

Disease	Cyclophosphamide	Cyclosporin
Antibody mediated		
Systemic lupus erythematosus	++	+
Goodpasture's syndrome	++	±
Wegener's granulomatosis	++	±
Pemphigus	+	
T-cell mediated		
Type I diabetes	±	++
Uveitis		++
Psoriasis		++

++, complete remission; +, partial remission; ±, inconsistent effect.

Limitations of immunosuppressive treatment

1) Not all patients respond.

2) The disease relapses a few months after cessation of the treatment.

3) Severe side effects of immunosuppressive drugs.

For example, cyclosporine is nephrotoxic and may give rise to malignancies

Surprisingly, the incidence of opportunistic infections due to treatment with cyclosporine and low dose methotrexate is lower than one would expect given the general, non-specific mode of action of these drugs. The reason for this is not clear.

8.5.2 Potential future treatment modalities, including selective and antigen-specific treatments

For organ specific autoimmune disease that is driven by a specific tissue antigen, antigen specific lymphocytes may become an appropriate target. As both cell mediated as well as humoral immune responses are controlled by T cells, antigen specific T cells are the most attractive candidates in both cases. For systemic autoimmune diseases a broader antigen-nonspecific type of suppression may be necessary. The Figure on the previous page shows potential molecular T cell targets and Table 8.7 summarizes the current state of development of various treatment modalities.

Table 8.7, Strategies for induction of selective immunosuppression to prevent or treat autoimmune diseases

Strategy	**Target cells**	**Information required**	**Approach**	**efficacy in disease models**	**Clinical trials in progress**
MHC blockade	antigen presenting cells	MHC class II molecule presenting the autoantigen	anti-MHC mAbs anti-MHC-peptide complex mAbs MHC antagonists	yes yes yes	no no no
CD4 blockade	$CD4^+$ T cells	none	anti-CD4 mAbs	yes	yes
TCR V_β-specific T-cell depletion	V_β-positive T cells	restricted V_β-usage by pathogenic T cells	anti-TCR V_β-mAbs	yes	no
Tolerance induction	autoreactive T cells	autoantigen	autoantigen in tolerable form soluble peptide-MHC complexes	yes yes	no no
TCR antagonism	autoreactive T cells	autoantigenic epitopes	autoantigen analogues	not tested	no

Induction of regulatory T cells	regulatory T cells	restricted TCR usage by pathogenic T cells	T-cell vaccination TCR peptides	yes yes	yes yes
		suppressor inducing T-cell epitopes of the autoantigen	suppressor-inducing autoantigenic epitopes	yes	no
			oral administration of the autoantigen	yes	yes

TCR, T cell receptor; **mAbs** monoclonal antibodies

Figure 1 : Intermolecular Help in the Induction of Anti-native (m)DNA Autoantibodies

Figure 2 : Grave's Disease

Figure 3 : Signal Integration by T cells

Figure 4 : Targets for Selevtive Immunointervention in Autoimmune Diseases

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Myelin MS

Multiple Sclerosis and related demyelinating diseases have been among of the unsolved neurological mysteries of our time. This common neurological disorder primarily affects young adults and is more prevalent in persons of Western European lineage living in temperate zones. Pathologically, the disease is characterized by demyelination, the loss of the myelin sheaths which cover and and protect neurons, with the result that various parts of the brain become inflammed, neurons die, and the glial cells which surround and nourish neurons wither or multiply pathologically. Common initial symptoms include weakness, numbness, tingling, spastic paraparesis, and sphincter disturbances. The disease is characterized by frequent relapses and remissions which lead to increasing disability, weakness, spasticity, impaired vision, and urinary incontinence. Approximately 20% of patients with multiple sclerosis experience aggressive, debilitating symptoms, while the remainder may live a relatively normal life.

In the past, treatments for multiple sclerosis (MS) have focused on the use of potentially toxic and immunosuppressive drugs such as steroids and cyclophosphamides. Even the American Medical Association Book of Drug Evaluations claims no specific long-term benefit of these drugs, in recognition of the fact that they may provide symptomatic relief but cannot prevent further relapses.

Two major theories of the cause of MS have been proposed. One is that MS is a viral disease of the central nervous system, the inflammatory response in the brain being an anti-viral immune response. The other is that MS is an autoimmune disease in which infiltrating T-cells recognize self-antigens in the myelin and attack normal tissue. These two possibilities are not mutually exclusive (autoimmune responses may be triggered by environmental factors such as viral infections, for instance); however, the inability to transfer the disease to primates or to isolate the virus from CNS tissue of MS patients, despite tremendous efforts, lends indirect support to autoimmune theory. This basic premise forms the scientific justification for the use of the myelin extract as an antigen therapy.

Physical Characteristics of Myelin

Myelin is a very important constituent of the white matter of the brain and the myelin sheath forms 50 per cent of the total dry weight. The myelin sheath is a greatly extended and modified plasma membrane that is wrapped around the nerve axon in a spiral fashion. Myelin acts as an electrical insulator surrounding the axon, the "wire" carrying the current in nerve conduction. This lipid-rich material contains high concentrations of cholesterol, phospholipids and plasmalogens. The basic proteins in myelin are immunologically active and may cause an autoantibody response.

The Peyer's patches in the intestine contain the immunological receptor sites which recognize myelin basic protein (MBP). When a glandular extract of myelin sheath is taken orally in a patient with multiple sclerosis, the protein appears in the epithelial cells that line the lower small intestine. As a person's T-cells circulate through the intestinal wall, complement cells that recognize MBP bind to these epithelial cells and are inactivated. Slowly, systemic immune tolerance to MBP emerges.

Immunolgical Correlates

60 Capsules HI2020

Each capsule contains Myelin Sheath Extract (Spinal Cord) 235mg

Suggested Use Take two capsules a day or as directed by a qualified health care practitioner.

Main Applications As reported by literature: -Treatment of MS. -Fibromyalgia.

Origin USA

Source Bovine spingomyelin. None hormone fed, free-range grazing animals from New Zeland.

Interactions None reported.

Pregnant / Nursing Has not been tested, best to avoid use. .

Complementary Products: -Magnesium Malate Forte HI2018 - Tryfonia HI2113 -ThinkWell HI2170 .

Mechanism of Action

Immunological tolerance is a state of immunologic unresponsiveness to a specific antigen after exposure to the agent. An effective and long-recognized method of inducing immunologic tolerance is the oral administration of the antigen, which was first demonstrated by Wells for hen's egg proteins in 1911. Orally-induced tolerance is a normal immune response that is used in the prevention of allergic reactions to food antigens, but it is only recently that it has been applied in the suppression of autoimmune response to a defined antigen. The application of oral tolerance to other models of autoimmune disease has recently received attention, including the suppression of type II (collagen-induced) arthritis, systemic lupus erythematosis, type I (autoimmune) diabetes, and uveitis. A human study involving therapy with oral myelin by Hafler and coworkers showed that antigen-specific suppressor T-cells are involved in actively suppressing the autoimmune response by secreting the immune mediator TGF-beta 1. Alternative modes of action, including the production of soluble factors in the serum and the formation of antigen-to- antibody complexes, have also been proposed.

MBP comprises 30% of the polypeptides of CNS myelin. Detection of MBP peptides in cerebrospinal fluid may indicate ongoing CNS demyelination. How MBP leaves its intracellular location to become accessible to auto-aggression lymphocytes within the CNS is a long-standing question. Fortunately, the treatment of an organ-specific autoimmune disease by oral tolerization often does not require knowledge of the inciting autoantigen, but only the oral administration of an autoantigen from the target organ.

The specificity of the orally-induced tolerance to MBP has been found to be strikingly species-dependent . For example, tolerance resulting from oral guinea pig MBP is effective in protecting rats against an MBP challenge and the same degree of specificity was observed for human MBP. However, attempting to orally tolerize rats against the self-antigen RMBP consistently fails. Bovine myelin has been shown to be a good choice for human usage.

Preliminary trials in humans provide exciting evidence for the effectiveness of oral antigen therapy in MS. Numerous investigators have already shown that oral myelin induces the presence of circulating MBP, and the T-suppressor cells and TGF-beta 1 responses consistent with other autoimmune therapies. Weiner et al administered either bovine myelin or a placebo protein to 30 MS victims. The active group had only half the rate of attacks of the controls. Brod et al, and other investigators, have shown similar results in animal models. Related approaches, using vaccination with the autoimmune T-cells themselves, T-cell receptor peptides, or Cop-1 (a synthetic analog of MBP), have also shown success, and support both the autoimmune theory and the oral tolerization approach.

It may be years before the large-scale trials required for this therapy to be approved by national medical authorities are completed, but the choice to pursue this option is available to individuals and their doctors now, in the form of Myelin MS.

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Nasal administration of myelin basic protein prevents relapsing experimental autoimmune encephalomyelitis in DA rats by activating regulatory cells expressing IL-4 and TGF-beta mRNA.

Bai XF, Shi FD, Xiao BG, Li HL, van der Meide PH, Link H.

Division of Neurology, Karolinska Institute, Huddinge University Hospital, Stockholm, Sweden.

This study explores nasal administration of myelin basic protein (MBP) as a potential means of inducing tolerance to relapsing experimental autoimmune encephalomyelitis (PR-EAE), an experimental multiple sclerosis (MS) model that was induced in DA rats by immunization with rat spinal cord homogenate and incomplete Freund's adjuvant. DA rats received a total dosage of 0, 6, 60, 600 micrograms/rat of bovine MBP on ten consecutive days prior to immunization. EAE with typical course was observed in control rats receiving only PBS nasally, and in rats receiving 6 micrograms/rat of MBP. Rats receiving 60 micrograms/rat of MBP developed acute EAE but no relapse during 60 days of observation post immunization (p.i.). Only one of eight rats receiving 600 micrograms/rat of MBP developed slight, transient EAE. This protection was confirmed at the histology level and was associated with decreased levels of MBP-reactive IFN-gamma secreting Th1-like spleen cells on day 13 and 60 p.i. Rats receiving 60 and 600 micrograms/rat of MBP showed decreased serum anti-MBP IgG2b antibody levels on day 60 p.i., and rats receiving 600 micrograms/rat of MBP had marginally increased anti-MBP IgG1 antibody levels in serum compared to control EAE rats. Cytokine mRNA profiles in central nervous system (CNS) and spleen mononuclear cells were evaluated. Dose-dependent reduction of TNF-alpha mRNA expression were observed both in CNS and in splenocytes. Increased IL-4 and TGF-beta mRNA expression were observed in CNS of low (6 micrograms/rat) and median (60 micrograms/rat) dose of MBP tolerized rats and in

splenocytes of rats tolerized with 600 micrograms/rat of MBP. We conclude that nasal administration of MBP in DA rat prevents EAE induced by immunization with whole rat spinal cord homogenate that, besides MBP, contains multiple antigenic myelin proteins. A mechanism involving MBP-reactive regulatory cells expressing IL-4 and TGF-beta mRNA acts as part in the induction of this tolerance.

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Cord blood contains high numbers of autoimmune T cells recognizing multiple myelin proteins and acetylcholine receptor.

Fredrikson S, Sun JB, Huang WX, Li BL, Olsson T, Link H.

Department of Neurology, Karolinska Institutet, Huddinge Hospital, Stockholm, Sweden.

To analyze Ag-specific T cell autoimmunity in the newborn, umbilical cord blood cells of newborns were investigated by an immunospot assay for occurrence and numbers of cells secreting IFN-gamma after short-term culture in presence of myelin basic protein (MBP), proteolipid protein, myelin associated glycoprotein, nicotinic acetylcholine receptor and the synthetic MBP amino acid sequences 1-20, 63-88, and 110-128. These Ag were chosen because they represent putative targets for autoimmune attack in multiple sclerosis and myasthenia gravis. Surprisingly, numbers of T cells recognizing MBP, proteolipid protein, MBP peptides, and acetylcholine receptor were high in cord blood of newborns compared to peripheral blood of patients with neurologic diseases. No immunodominant T cell epitope could be discerned among the Ag included. The responses to purified protein derivate and PHA were lower among cord blood cells than peripheral blood cells of adults. Parallel enumeration of autoimmune T cells in cord blood and peripheral blood obtained from corresponding mothers at delivery, revealed that the high cell numbers in newborns were not a result of contamination from the mothers blood. The high numbers of T cells recognizing nervous system myelin proteins and acetylcholine receptor in cord blood could have importance for the mechanism and timing of tolerance induction, and also reflect excessive myelination and receptor maturation at birth.

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